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10/580,237	05/23/2006	Christopher Penney	GRT/4141-20	1942

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,237	PENNEY ET AL.	
	Examiner	Art Unit	
	/Venkataraman Balasubramanian/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-24 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-24 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Upon further consideration, due to an error in rejected claims pointed out by the applicants, the previous office action is vacated and the following office action is made.

The preliminary amendment, which included amendment to claims 4, 6-9 and 21-24, filed on 5/23/2006, is made of record. Claims 1-24 are pending.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on 5/23/2006, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Recitation of "B=0" in claim 1, renders claim 1 and its dependent claims indefinite as it is not clear what is the nature of B. Note B is not an index but appears to be group. An appropriate correction is needed. Also see claim 3.

2. Recitation of " Y is not necessarily equal to Y' " and "A is not necessarily equal to C" in claim 1 renders claim 1 and its dependent claims indefinite as it is not clear what is intended. The phrase "not necessarily equal to" is vague and unclear. In addition, there is no definition of Y or Y'. Furthermore, A and C are independent variable groups and

not defined as relational variable group. The same applies to the index n, which is also recited as "not necessarily equal to m". Also see claim 2 for the same.

Replacement of "formulas" in claim 1 with "formulae" is suggested.

3. Claim 5 is missing "and" before the last species.

4. Claims 6 and 8 are duplicate of claim 1. A compound is compound irrespective of its attributes. Claim 6 and 8 provide an attribute to compound of claim1 with no material variation. Compound of claim 1 is clearly defined by formula therein and the compounds of claim 6 and 8 also have the same genus of formula of claim 1. Hence, they are duplicates of claim 1. See Intirtool, LTD. V. Texar Corp., 70 USPQ2D 1780. Note court held that "In general, a claim preamble is limiting if recites essential structure or steps or if it is necessary to give" life, meaning, and vitality to claim.'.... However, if the body of the claim describes a structurally complete invention such that deletion of the preamble phrase does not effect the structure or steps of the claimed invention,' the preamble is generally not limiting unless there is clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art.""

Instant claims 6 and 8 are compound claims and the compound is clearly defined by a structure shown in formula of claim 1. Omission of the attributes (that they can noncovalently bind to antibodies) to the compound of genus of claim 1 would not alter the structure of these compounds.

Again in claim 7, no weight is given to this attribute and claim 7 is treated as compound claim which further limits claim 1.

5. Recitation of "at least one compound according to claim 1" in claim 9 renders claim 9 and its dependent claims indefinite. The said phrase implies that, besides the said compound of claim 1 as active ingredient, the composition can have other undefined active ingredients. Replacement of " at least one" by "one or more" is suggested.

6. Claims 21 and 24 provides for the use of compound of formula shown in claim 1, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for rheumatoid arthritis, does not reasonably provide enablement for any or all autoimmune diseases or TNF-α mediated disorders/diseases generically embraced in the instant claims 16-20. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following reasons apply.

The instant claims are drawn to "treating a patient with autoimmune disease ".

Instant claims, as recited, are reach through claims. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of TNF-α activity by the instant compounds, instant claims reaches through inhibiting and treating any or all autoimmune diseases in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of TNF-α, based on limited assay, it is claimed that treating any or all diseases autoimmune diseases including any or all inflammatory diseases or disorders in general, for which there is no enabling disclosure.

The "autoimmune diseases" are a process that can take place in virtually any part of the body. There is a vast range of forms that it can take,' causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are hundreds such diseases, which have fundamentally different mechanisms and different underlying causes. Thus, the scope of claims is extremely broad.

The same applies to inflammatory diseases. Similarly, enablement for the scope of "inflammation" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments

for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neurophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the

non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

The scope of the claims includes not only any or all conditions but also those condition yet to be discovered for which there is no enabling disclosure. In addition, the scope of these claims includes, besides rheumatoid arthritis, treatment of various specific diseases such as psoriatic arthritis, psoriasis, Crohn's disease, inflammatory bowel disease, ankylosing spondylitis, Sjogren's syndrome, Still's disease (macrophage activation syndrome), uveitis, scleroderma, myositis, Reiter's syndrome and Wegener's syndrome, which is not adequately enabled solely based on the inhibiting expression of TNF-α activity of the compounds provided in the specification pages 25-29 and 59-72 . The instant compounds are disclosed to inhibit TNF-α activity and it is recited that the instant compounds are therefore useful in treating any or all diseases where TNF-α activity is implicated, for which applicants provide no competent evidence. Furthermore, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. That a single class of compounds can be used to treat all diseases embraced in the claims is an incredible finding for which applicants have not provided supporting evidence. Moreover many if not most of diseases such as, multiple sclerosis, lupus, AIDS, malignant diseases etc. are very difficult to treat and at present there is no known drug, despite the fact that there are many drugs, which can be used for inflammatory condition or inhibiting TNF-α activity. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288.

Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Haraoui, B., The Journal of Rheumatology, Volume 32, Supplement 74, 3-7, 2005. See entire document especially Summary at page 6. See also Bongartz., et al., JAMA, Vol. 295(19), 2275-2285, 2006 for anti TNF antibody therapy, Seko et al., Autoimmunity Reviews, 5, 299-305, 2006 and Moller et al., Springer Semin. Immun., 27, 391-408, 2006. Note all of these reference calls for further experimentation.

Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.". Clearly that is the case here.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating all autoimmune diseases that require inhibition of TNF-α activity.

2) The state of the prior art: Recent publications expressed that treating autoimmune disease by the inhibition of TNF-α is still exploratory. See Haraoui, B., Bongartz., et al., Seko et al., and Moller et al., cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of inhibiting TNF-α activity are unpredictable and at best limited to modulation of rheumatoid arthritis.

6) The breadth of the claims: The instant claims embrace any or all condition including those yet to be related to expression of TNF-α activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 21 and 24 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under

35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Lowik et al., WO 01/42228.

Lowik et al., teaches several triazines compounds and their use as affinity ligands on solid supports. See pages 1-3 for description of the invention and Schemes 1-8 for various triazines made and attached to solid support. See pages 4-8 for examples 1-5 and pages 8-19 for compounds 1-53b. Especially see example 2 and various examples in Schemes (Figures 3a, 3b, 6 and 7).

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Atkinson et al., GB 2 053 926.

Atkinson et al., teaches various triazine compounds useful as affinity chromatography materials attached to a solid support. See page 1-2, especially page 2, lines 4 0-45. See table 1, Note Procion Red HE-3b is taught as ligand for attachment to solid support.

Claims 1-4 and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Dore et al., GB 2 149 808.

Dore et al., teaches various triazine compounds useful as dyes for dyeing various materials. See entire document especially see example 61 and 91b.

Claims 1-4 and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Adam et al., EP 0 122 458.

Adam et al., teaches various triazine compounds useful as dyes for dyeing various materials. See entire document especially see examples 72-93.

Claims 1-4 and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Cipolli et al., EP 0 542 374.

Cipolli et al., teaches various triazine compounds useful for incorporating into various materials. See entire document especially Table 1, examples 1-24.

Claims 1-4 and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Lavery et al., US 6,482,255.

Lavery et al., teaches various triazine compounds useful for ink-jet printing. See entire document especially examples 1-27.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dore et al., GB 2 149 808 or Adam et al., EP 0 122 458 or Cipolli et al., EP 0 542 374 or Lawery et al., US 6,482,255 in view of Lowik et al., WO 01/42228 and Atkinson et al., GB 2053 926.

Teachings of Dore et al., Adam et al., Cipolli et al., Lawery et al., Karrer et al., and Atkinson et al., as discussed in the above 102 rejections are incorporated herein. As noted above, Dore et al., Adam et al., Cipolli et al., Lawery et al., and Karrer et al., teach several triazines compounds and their attachment to various support materials. But they did not teach the use of these triazines for affinity chromatography of proteinaceous materials.

The secondary reference, Lowik et al., teaches several triazines bound matrix for affinity chromatography and Atkinson et al., teaches use of several triazines in affinity chromatography. These two references teach equivalency of the various triazines and their bound form for affinity chromatography. Thus, it would be obvious to one trained in the art to use polymer bound triazine compounds for affinity chromatography of proteins in view of the equivalency teaching outlined above. See In re KSR International vs Teleflex Inc., 82 USPQ2d 13-85, 1397 (2007).

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

10/25/2007